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CARDIAC AND PHYSICO-CHEMICAL RESPONSES TO XYLAZINE AND FENTANYL ANALGESIA IN *Bubalus bubalis*

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ABSTRACT

The minor surgical intervention and safe restraining requires sedation and analgesia especially in furious animals like buffaloes which can be achieved by using proper combination of sedative and analgesic drugs. The combination of xylazine with opioids is an effective way to achieve sedation and analgesia in cattle and horses. Six apparently healthy buffaloes having minor wounds were included in the present study. The sedation was accomplished by fentanyl (5 µg per kg b.wt) plus xylazine (0.05 mg per kg b.wt) intravenously. Physiological, hematobiochemical and electrocardiographic parameters were observed at different time interval after the administration of drugs. Following the administration of medicine, there was a significant reduction in heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, hemoglobin, and packed cell volume. Respiration rate increased significantly at 30 minutes interval. PR interval and QT interval increased significantly at 20 minutes and 15 minutes respectively of the observation period, whereas a significant increase in the duration of ST segment was noticed from 15 minutes to 30 minutes. The present study revealed that the drug combination has no deleterious effects on cardiopulmonary, hematobiochemical and physiological parameters during the observation period.

Keywords: *Bubalus bubalis*, buffaloes, xylazine, fentanyl, cardiac rhythm, analgesic, sedative

INTRODUCTION

For any surgical intervention, immobilization of the animal, muscular relaxation, unconsciousness and freedom from pain are mandatory (Thurmon *et al*., 1996) and these requirements are met with general anesthesia. General anesthesia becomes inevitable in certain more complicated procedures like diaphragmatic Herniorrhaphy, thoraco-pericardiotomy, repair of ruptured suspensory ligaments, orthopedic surgery, keratoplasty and repair of ventral hernia etc. But minor surgical intervention can be effectively and safely managed by effective sedatives and analgesics. Prior to inducing anesthesia, domestic ruminants are typically not administered with anticholinergic

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medications. Except when given at higher doses more frequently, they do not consistently reduce salivary secretions. Pentobarbital, chloral hydrate, diazepam, midazolam, and acepromazine are some of the classic medications used to sedate and/or tranquillize ruminants. As a more strong sedative in ruminants than in horses, xylazine is frequently used to sedate or, in higher doses, restrain ruminants (Greene, 1999). To make handling of furious animals during minor surgical procedures safer, sedation is needed. Different drugs like triflupromazine, aceproazine, xylazine, detomidine, diazepam and midazolam have been used in buffaloes (Hall *et al*., 2001).

In recent years butorphanol has been combined with xylazine and other more selective α_2 agonists to improve analgesia and sedation. Xylazine, butorphanol combination has been used for sedation and analgesia in the horses, elephant, ruminants dogs, cats and laboratory animals (Faulkner *et al*., 1992) 6- to 9-mo-old, bull calves (214 +/- 19 kg. Significant reduction in the requirement of local anesthesia after combined use of xylazine and butorphanol to achieve analgesia in cows subjected to abdominal surgery has been observed (Levine *et al*., 1992). Different species react differently to α_2 adrenergic receptor subtypes in the CNS. Ruminants most notably have 2D adrenergic receptors which makes them particularly sensitive to sedating effects of α_2 adrenergic agonists. Activation of α_1 adrenergic receptors in CNS will cause arousal, agitation, increased locomotors activity and vigilance (Sinclair, 2003). Although this is not a wanted effect, it explains why, in same animals or with some drugs that have more α_1 receptors activity, an animal may show paradoxical excitements or movements.

Fentanyl is a synthetic opioid that is extremely lipid soluble and has a short half-life. Compared to morphine, fentanyl's single intravenous dose has a quicker onset and a significantly shorter duration of action. Peak analgesic effects start to take action in around five minutes and last for about thirty minutes. (Gutstein and Akil, 2001). The medicine's therapeutic effects end rapidly due to quick redistribution of the medicament to inactive tissue locations like fat and skeletal muscles, which causes a drop in plasma concentration. Fentanyl administration has side effects that are comparable to those of other μ-opioids that are full agonists. When administered intravenously, fentanyl frequently produces excellent cardiovascular stability and doesn't trigger histamine release. (Gutstein and Akil, 2001). Sedation is generally required for minor surgical intervention in buffaloes. There is paucity of literature on the effect of xylazine and fentanyl on electrocardiographical parameters. The aim of the present study was to study the electrocardiographic and cardiopulmonary alteration associated with the sedative drugs to ascertain the effects of these drugs on vital parameters.

MATERIALS AND METHODS

Six clinically apparently healthy buffaloes having minor wounds of one to three years of age, presented in veterinary clinical complex, Bihar veterinary college, Patna, Bihar were used in this study. All the animals were stall fed and had free access to food and water. The clinical status of the animal was assessed by recording heart rate, respiration rate, rectal temperature, urea nitrogen, Creatinine, Mean arterial pressure, Diastolic blood pressure, Systolic blood pressure and Electrocardiography. In the present study sedation

was accomplished by fentanyl (5 µg per kg b.wt) plus xylazine (0.05 mg per kg b.wt) intravenously. Depending on the following parameters, the various treatments were assessed:

Physiological observations

The following parameters were recorded before administration (0 minute) and at 5, 10, 15, 20 and 30 minutes after administration of sedative agents. The heart rate was measured using stethoscope auscultation (beats per minute). The respiratory rate (breaths per minute) was recorded by observing the thoracic excursions. The rectal temperature (^{o}C) was recorded by a clinical thermometer.

Hematological observations

The blood sample (1 ml) was collected from jugular vein in clean, dry vials containing heparin at time 0 (base line), 15 and 30 minutes after administration of fentanyl and xylazine. Hemoglobin was estimated using hellige sahli's hemoglobinometer. The value was expressed in g/L. The packed cell volume was estimated by using microhematocrit method (Schalm, 1986). The value was expressed in L/L. Total leucocyte count was determined by using a hemocytometer with improved Neubaur's counting chamber and its values were expressed in $X10^{9}$ /L. For differential leukocyte count blood smears were stained with leishman's stain and examined under oil immersion for cellular differentiation in percentage of different leukocytic components.

Biochemical observations

The blood sample (10 ml) were collected from the jugular veins in clean, dry test tubes containing heparin (sodium fluoride for glucose) at time 0 (base line) 15 minutes and 30 minutes after the administration of xylazine and fentanyl for separation of plasma. Blood Urea nitrogen was determined using diacetyl monoxime (DAM) and the values were expressed in mmol/L (Natelson, 1961). Glucose was estimated by O' toluidine method and the value were expressed in µmol/L.

Haemodynamic Observation

The cuff of the non-invasive blood pressure monitor was applied around the metatarsal regions for monitoring systolic, diastolic, and mean arterial blood pressure. The following parameters were evaluated during the whole period of observations. Mean arterial pressure (mmHg); Diastolic blood pressure (mmHg), Systolic blood pressure (mmHg) was recorded at time 0 min (base line) and at 5, 15, 20 and 30 minutes after administration of xylazine and fentanyl.

Electrocardiography

Subcutaneous needle electrodes were placed at the posterior border of scapula and at the 5th costochondral junction (base apex lead) for electrocardiography. A standards base apex lead electrocardiogram was recorded at 1 mv and 25 mm/second paper speed at the same interval as recorded in blood pressure. The electrocardiogram was analyzed for the duration and amplitude of P-wave, QRS complex, T-wave, P-R and Q-T intervals and rhythm.

Statistical analysis

One-way ANOVA was used to compare the means at different time intervals (Snedecor and Cochran, 1994).

RESULTS AND DISCUSSIONS

A significant (P<0.05) decrease in HR and RR was observed in Group H1 at 5 minutes after administration of fentanyl and xylazine. α_2 agonists and fentanyl combinations resulted in significant decrease in heart rate immediately after the administration of xylazine and fentanyl. These changes were related to the CNS sedative and the autonomic and peripheral vascular effects of α_2 agonists. Similar findings were reported earlier demonstrating that after administration of epidural romifidine in cattle and transdermal administration of fentanyl in goats respectively (Marzok and El-khodery, 2016; Burke *et al*., 2017) randomized study. SETTING Preclinical Testing Facility at a University Teaching Hospital. ANIMALS Thirty-four adult female Boer-cross goats. INTERVENTIONS Goats underwent surgery as part of a concurrent orthopedic research study. Twelve hours prior to surgery, each goat received a TFP (target dosage of 2.5 μg/kg/h. Changes in the heart rate and rhythm are generally caused by effects of the drug on CNS, autonomic nervous system or cardiac automaticity and the compensatory response to cardiovascular (Feng *et al*., 2019). Hypotension is attributed to bradycardia and vasodilation due to the estimation of central α_2 adrenoceptors, peripheral sympathetic action and enhanced parasympathetic outflow (Kumar *et al*., 2014)haematobiochemical and haemodynamic effects of propofol and ketamine total intravenous anaesthesia (TIVA. The biphasic response of blood pressure was not observed in the present study probably due to the synergistic effects of α_2 agonists and fentanyl causing hypotension predominantly. Similar findings were reported in dogs undergoing orthopedic surgery of pelvic limbs under epidural administration of neostigmine alone or in combination with morphine (Marucio *et al*., 2014) Decrease in respiration was observed in this study during the sedation period. Respiratory depression associated with α_2 adrenergic agonists might be secondary to the central nervous system depression produced by α adrenoceptors stimulations (Sun *et al*., 2017) or due to direct depression of the respiratory centers by pre anesthetics (Kumar *et al*., 2014)haematobiochemical and haemodynamic effects of propofol and ketamine total intravenous anaesthesia (TIVA. Observation of the present study are in well accordance with the finding of Pagliosa (Pagliosa *et al*., 2015). A non-significant decrease in rectal temperature was noticed.

During the whole observation periods and this could be ascribed to a decline in skeletal muscle tone, decreased metabolic processes, relaxation of the muscles, as well as depression of thermoregulatory zones (Malik *et al*., 2011). In this study a highly significant decrease in hemoglobin, PCV, TLC was noticed at 20 minutes in all the animals. This could happen because of an accumulation of blood cells in circulation triggered by sympathetic activity in the spleen or other reservoirs. Similar results following medetomidine epidural treatment in goats have also been documented (Kinjavdekar *et al*., 1999). Malik also have reported the similar findings after administration of medetomidine-butorphanol and midazolam butorphanol in buffaloes (Malik *et al*., 2011). Increase in lymphocyte and neutropenia were observed in this study, this could result from stress set forth by the injections of xylazine and fentanyl and the ensuing stimulation of the adrenal glands. Similar finding has been reported after medetomidine-ketamine administration in goats (Kumar *et al*., 2014; Azari *et al*., 2014)no. 1 (2006. No significant change in biochemical parameters *i.e.* glucose, urea nitrogen and creatinine were

recorded in the present study. But the value of glucose was higher than the base value at 10 minutes. Similarly, administration of xylazine in cattle has also been reported to cause hyperglycemia (Hsu and Hummel, 1981).

For the entire length of the observation period, a significant reduction in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) was observed. Intravenous administration of α_2 adrenergic agonists results in a transient initial hypertension followed by a prolonged hypotension (Sun *et al*., 2017). The biphasic response of blood pressure after intravenous administration of α_2 adrenergic-agonists was not observed in the present study, which might be due to the fact that the initial recording of blood pressure was made 5 minutes after administration of drugs and only second phase of the response (hypotension) could be recorded. An initial hypertension is triggered by the stimulation of post-synaptic α-1 and α-2 adrenoceptors in the smooth muscles of the vascular system (sympathomimetic effect). The stimulation of central α-2 adrenoceptors at the brain stem and spinal cord has been linked to a subsequent decrease. (Sun *et al*., 2017). As a consequence of bradycardia, vasodilatation, stimulation of the central α-2 adrenoceptors, peripheral sympatholytic activity, and increased parasympathetic outflow, hypotension ensues on. (Marzok and El-khodery, 2016) divided randomly into four groups (three experimental and one control; n=6. Following systemic romifidine dosing in goats, hypotension has also been observed. (Kumar *et al*., 2014) haematobiochemical and haemodynamic effects of propofol and ketamine total intravenous anaesthesia (TIVA).

In electrocardiography P- wave duration, QRS-complex, T-wave duration and T-wave amplitude did not reveal any significant change at different time intervals. Similar outcomes have been documented following medetomidine injection in goats (Hugar *et al*., 1998), nonetheless, following medetomidine spinal delivery in goats, there was no difference in the P-wave's duration or amplitude (Singh *et al*., 2013) analgesic and clinical effects of xylazine, medetomidine and dexmedetomidine with fentanyl as pre-anaesthetics in water buffaloes and to compare the dose-sparing effect of xylazine, medetomidine and dexmedetomidine on thiopental for induction and isoflurane for maintenance of anaesthesia in water buffaloes. Six male water buffaloes randomly received intravenous fentanyl (5.0 µg/kg body weight. No significant difference in ventricular depolarization time (QRS complex) was observed in all the groups of the present study. Similarly no appreciable changes in ventricular depolarization time were recorded by Hugar after medetomidine administration in goats (Hugar *et al*., 1998). Kinjavdekar also reported no change in duration and amplitude of QRS complex after spinal administration of medetomidine in goats (Kinjavdekar *et al*., 1999). QS pattern is seen in all the animals of the present study. The deviation and inconsistency of T-wave might be due to transient change in acid base balance on account of retention of CO_2. An increase in T-wave after administration of medetomidine and ketamine in goats was earlier reported (Hugar, 1993). Since α-2 adrenergic agonists have been linked to a variety of arrhythmias, the electrocardiograms of all the animals exhibited sinus bradycardia. Bradycardia and A-V blocks most likely result from elevated vagal activity brought on by xylazine's vasopressor action (Kumar *et al*., 2014) haematobiochemical and haemodynamic effects of propofol and ketamine total intravenous anaesthesia (TIVA). The occurrence of elevation of S-T segment, T-wave

Table 1. Physiological and electrocardiographical parameters of buffaloes at different time intervals before and after administration of Xylazine and fentanyl (Mean±SE).

Parameters	Time interval (minutes)					
	0	5	10	15	20	30
Heart rate (beats/min)	40.00±2.76	25.33** ±1.11	26.83*±1.44	26.80**±0.79	26.33*±0.88	28.00*±1.87
Respiration rate (breath/min)	8.33±0.33	5.66*±0.61	7.66±1.47	11.00±1.69	11.50±1.28	13.66*±1.35
Rectal temp (^{0}C)	36.22±0.33	36.23±0.48	36.11±0.59	35.58±0.63	35.58±0.57	35.44±0.86
Systolic blood pressure (SBP in mmHg)	134.00±5.77	94.83**±5.21	89.33**±5.30	84.50**±6.01	87.16**±7.88	95.83*±8.15
Diastolic blood pressure (DBP in mmHg)	100.50±3.62	61.83**±3.84	48.66**±5.54	49.83**±5.66	50.50**±8.63	59.33*±9.07
Mean arterial blood pressure (MAP in mmHg)	116.00±3.92	77.33**±3.91	68.66**±3.61	63.16**±5.38	68.33**±8.08	75.33**±7.67
P-wave duration (sec)	0.106±0.008	0.106±0.013	0.106±0.008	0.106±0.008	0.113±0.006	0.093±0.013
P-wave amplitude (mv)	0.183±0.001	0.183±0.016	0.183±0.016	0.200±0.00	0.166±0.021	0.133±0.021
QRS Complex duration (sec)	0.140±0.008	0.146±0.008	0.146±0.008	0.146±0.008	0.146±0.008	0.153±0.012
T-wave Duration (sec)	0.200±0.017	0.220±0.017	0.246±0.019	0.200±0.017	0.193±0.012	0.213±0.016
T-wave Amplitude (mv)	0.433±0.102	0.583±0.070	0.566±0.049	0.416±0.030	0.316±0.047	0.416±0.060
P-R interval duration (sec)	0.266±0.008	0.273±0.006	0.280±0.014	0.273±0.019	0.300**±0.008	0.273±0.006
Q-T interval duration (sec)	0.626±0.030	0.686±0.033	0.733±0.045	0.813*±0.028	0.820±0.026	0.806±0.031
S-T segment duration (sec)	0.346±0.024	0.353±0.021	0.393±0.019	0.466*±0.028	0.480*±0.034	0.460*±0.030

*Significantly different from base value ($P<0.05$). **Significantly different from base value ($P<0.01$).

Table 2. Haematobiochemical parameters of buffaloes at different time interval before and after administration of Xylazine and fentanyl (Mean ± SE).

Parameters	Time interval (minute)		
	0	15	30
Haemoglobin (g/L)	120.06±0.13	101.16±0.39**	98.33±0.29**
PCV (L/L)	0.37±0.085	0.32±0.105*	0.31±0.081**
TLC (X10^9/L)	13.9±1.37	10.40±1.25	9.96±1.44
Lymphocyte (%)	60.16±1.72	59.66±1.38	57.66±1.47
Neutrophil (%)	30.83±0.40	32.50±0.88	33.16±0.76
Glucose (mmol/L)	9.23±0.48	9.44±0.81	8.99±0.58
Creatinine (µmol/L)	144.42±5.84	142.53±4.65	156.65±2.28
Urea nitrogen (mmol/L)	9.30±0.68	9.18±0.87	10.34±0.90

*Significantly different from base value (P<0.05), **Significantly different from base value (P<0.01).

changed wandering pacemakers and ectopic pacing in sheep during thiopentone-halothane anesthesia have been reported (Peshin *et al*., 1985). Except for modest T wave variations in the heart rhythm, none of the aforementioned abnormalities were seen in the present investigation. In this study P-R interval increased after administration of xylazine and fentanyl. The P-R interval changes were dependent on conduction velocity between SA node and AV conduction system. Venugopalan reported that prolonged P-R interval would indicates a decrease in conduction velocity within the arterial muscles, the SA conduction system or both (Venugopalan *et al*., 1994). In this study, xylazine may have extended the PR interval and slowed conduction between the SA node and AV conduction system or both. Increased Q-T intervals were observed in this study. Following the administration of benzodiazepines to calves, similar results have been recorded (Mirakhur *et al*., 1988; Willium *et al*., 1992). The sum of ventricular depolarization, which reflects ventricular systole, determines Q-T intervals. Sympathetic neurons control the P-R and Q-T intervals, and they might or might not be active at the same instance.

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